B. *Sulfamethoxydiazine (Sulfameter, Sulla)*

C. *Sulfadimethoxine (Madribon)*

D. *Sulphormethoxine*—Very long-acting; therapeutic blood levels for 1 week.

V. POORLY ABSORBED SULFONAMIDES: for local use in the intestinal tract only.

A. *Succinylsulfathiazole (Sulfasuxidine):*

1. Dosage—3.0 Gm q 4 h p.o.

2. Maximum effect usually not achieved until 7th day of therapy.

B. *Phthalylsulfathiazole (Sulfathalidine):*

1. Dosage—1.5 Gm q 4 h p.o.

2. Double this dosage in the presence of diarrhea.

3. Effect produced in 5-7 days.

C. *Para-nitrosulfathiazole (Nisulfazole):* Used only for intrarectal instillation in treatment of proctitis or non-specific colitis.

VI. TOPICAL SULFONAMIDES:

A. *Mafenide (Sulfamylon):* Used on skin as 10% cream. Unlike other sulfonamides, effective in presence of pus and necrotic tissue and does not sensitize readily when used topically. Of value in prevention and therapy of burn infection due to *Pseudomonas.*

B. *Ophthalmic preparations:* Sodium sulfacetamide (Sulamyd) and sulfisoxazole diolamine are the only products suitable for topical use in the eye; they are available as solutions (30%) and ointments (10%).

C. *Vaginal preparations:* These include sulfisoxazole and triple sulfonamide combinations made up as creams or tablets. They are used in nonspecific vaginitis and cervicitis.

VII. SULFAPYRIDINES:

A. *Sulfapyridine:* Too toxic for general use, but best drug available for dermatitis herpetiformis.

B. *Salicylazosulfapyridine (Azulfidine):* Of value in ulcerative colitis, particularly in preventing relapse. Value in regional enteritis less well established.

VIII. SULFONAMIDES IN GENERAL:

A. Desired peak blood level—8-15 mg/100 ml (except poorly absorbed compounds).

B. Mode of action—bacteriostatic.

IX. TOXICITY AND SIDE EFFECTS:

A. Fever

B. Rash, urticaria

C. Cyanosis, methemoglobinemia

D. Nausea, vomiting, diarrhea

E. Hepatitis, jaundice

F. Hematuria, albuminuria, crystalluria, toxic nephritis.

G. Headache, mental depression, psychosis, peripheral neuritis.

H. Leukopenia, agranulocytosis, purpura, aplastic anemia, hypoprothrombinemia, hemolytic anemia.

I. Severe hypersensitivity reactions — anaphylaxis, periarteritis nodosa and other collagen diseases, Stevens-Johnson syndrome.

X. PRECAUTIONS:

A. Keep careful record of urine output — try to maintain output of at least 1200-1500 ml/24 hrs.

B. Alkalinization of urine—sodium bicarbonate (12-15 Gm/day) may be used for this purpose when full systemic doses of sulfonamides are used, when there is difficulty in being sure of adequate fluid intake and output, and when such adjunctive therapy is not contraindicated.

C. Check fresh urine specimens for RBC's, albumin and sulfa crystals.

D. Weekly blood counts.

ANTIBIOTICS AND ANTIBACTERIALS, GENERAL

SYDNEY M. FINEGOLD, M.D., AND ALVIN DAVIS, M.D.

I. PENICILLIN G (Benzylpenicillin):

1. *Spectrum and Uses:* Highly active against Gram-positive cocci other than beta lactamase-producing staphylococci; Gram-negative cocci; Gram-positive bacilli; fusiforms and some other Gram-negative anaerobic bacilli; and (in high dosage) *Proteus mirabilis.* Oral penicillin G is useful in many urinary tract infections due to *E. coli* and *P. mirabilis.*

2. *Types of Preparations, Route of Administration and Dosage:*

a. *Crystalline aqueous penicillin G:*

(1) Peak blood levels — generally 1-2 units/ml for each one million units intramuscular/day.

(2) Probenecid (Benemid) 0.5 Gm q 6 h will usually raise levels 1½ to 2 times.

b. *Procaine penicillin G suspended in oil or water:*

(1) With single intramuscular dose of 300,000 to 600,000 units, peak serum levels are usually 0.75 unit/ml or less and serum concentrations of at least 0.04 unit/ml (adequate for highly sensitive organisms such as pneumococci and Group A beta-hemolytic streptococci) persist for from 20 to 24 hours. Frequency of administration depends on preparation and dosage used.

(2) Increasing dosage primarily prolongs duration of blood level rather than raising peak level; the usual daily maximum should be 1.2 million units.

c. *Procaine penicillin G in sesame oil and 2% aluminum monostearate:*

A single 200,000 unit dose behaves much like procaine penicillin, but 600,000 unit doses result in levels of 0.03 units/ml or higher for more than 90 hours.

d. *Benzathine penicillin G (dibenzylethylenediamine dipenicillin G, DBED, Bicillin):*

(1) Very insoluble salt. 300,000 unit dose intramuscularly gives levels above 0.03 unit/ml for over 5 days with peak levels above 0.15 unit/ml uncommon at any time. Doses of 600,000 units and 1,200,000 units intramuscularly result in prolongation of levels to 12 and 28 days, respectively. (The oral form is poorly absorbed and should not be used.)

(2) Chiefly useful as a prophylactic agent and in the treatment of early syphilis.

(3) Painful on injection. Allergic reactions, when they occur, may be severe and prolonged.

e. *Oral penicillin G:*

For urinary tract infections, 400,000 units q 6 h.

3. *Toxicity, Side Effects, and Precautions:*

a. Central nervous system toxicity may occur when unusually high doses are used and/or impaired renal function exists.

b. The amount of potassium injected must be considered when very large doses of crystalline aqueous potassium penicillin are used in the presence of impaired renal function. Each 15 million units supplies 975 mg (25 mEq) of potassium.

c. Allergic reactions ranging from minor skin reactions to anaphylactic shock and death occur. The best prophylaxis is a careful history combined with discriminate use of this drug. The usual skin tests and conjunctival tests with penicillin G are unreliable. Use of penicillinase (Neutrapen) for treatment of penicillin allergy should be condemned because there is no proof of its effectiveness and because it may actually increase the hazard.

d. Hemolytic anemia, neutropenia.

4. *Mode of Action:* Bactericidal.

II. ALPHA-PHENOXY-PENICILLINS:*

A. *Phenoxymethyl penicillin (penicillin V, Pen-Vee, V-Cillin):* This compound is better absorbed on oral administration than penicillin G and is more acid stable. The antibiotic spectrum of the two agents is similar. Both are susceptible to staphylococcal beta lactamase. Most infections which will respond to oral therapy can be treated with 250-500 mg q 8 h. Infections such as osteomyelitis or subacute bacterial endocarditis (when they can be treated orally) require >50-1,000 mg q 4-6 h. Penicillin V is not ordinarily useful for therapy of urinary tract infections.

B. *Phenoxyethyl penicillin (phenethicillin, Syncillin, Maxipen, Chemipen, Broxil, Dargil, Alpen):* This compound is very similar to penicillin V.

III. BETA LACTAMASE-RESISTANT PENICILLINS:*

A. *Methicillin (Staphcillin, Celbenin, Dimocillin):*

1. *Spectrum and Uses:* Active vs staphylococci resistant to penicillin G (beta lactamase-producers). Distinctly inferior to penicillin G vs. other organisms.

2. *Routes of Administration and Dosage*

a. Intramuscularly 1 Gm q 3-6 h.

b. Intravenously 1-4 Gm q 4-12 h (12 Gm or more/day in severe infections). It is best given in 50-100 ml over a 30 minute period q 4-6 h. (The drug is relatively unstable, particularly at acid pH's. Make up just before use.)

*These agents exhibit cross-allergenicity with penicillin G. Probenecid blocks excretion of all penicillins. All are bactericidal.

3. *Toxicity, Side Effects and Precautions*

a. Sensitivity reactions, as with penicillin G.

b. Renal damage (hypersensitivity?) — fever, albuminuria, pyuria, hematuria, oliguria to anuria, nitrogen retention, edema, and eosinophilia may occur. This is apparently reversible, but complete recovery may take months.

c. Bone marrow depression (neutropenia) occurs occasionally.

d. Hemolytic anemia.

e. Each 4 Gm of drug supplies 230 mg (10 mEq) of sodium (drug supplied as sodium salt).

4. *Miscellaneous.* Moderately resistant staphylococci have been isolated rarely. When other agents are to be administred simultaneously, they should be given separately rather than being mixed with the methicillin.

B. *Oxacillin (Prostaphlin, Resistopen):*

1. *Spectrum and Uses:* Similar to methicillin, but somewhat more active on a weight basis. There is greater protein binding with this agent.

2. *Routes of Administration and Dosage:*

a. Oral—not recommended (cloxacillin or dicloxacillin are preferred oral agents.

b. Intramuscularly—0.5-1.0 Gm q 4 h.

c. Intravenously—0.5 Gm or more q 4 h. May be administered by method described for methicillin.

3. *Toxicity, Side Effects and Precautions:*

a. Sensitivity reactions as with penicillin G.

b. Neutropenia (rare).

c. Reversible SGOT elevations are occasionally noted.

4. *Miscellaneous* — cross-resistance with methicillin. Greater amount of biliary excretion than with methicillin. Not suitable for treatment of meningitis.

C. *Cloxacillin (Tegopen):*

1. *Spectrum and Uses:* Same as for oxacillin.

2. *Routes of Administration and Dosage:* Available only for oral use. Dosage is 0.5-1.0 Gm q 6 h.

3. *Toxicity, Side Effects and Precautions:*

a. Same as for oxacillin.

b. Nausea, epigastric distress, diarrhea, bitter taste.

4. *Miscellaneous:* Preferred over oral oxacillin because of better absorption and thus higher and more prolonged blood levels. Not suitable for treatment of meningitis.

D. *Dicloxacillin (Dynapen, Veracillin):*

1. *Spectrum and Uses:* Same as for oxacillin.

2. *Routes of Administration and Dosage:* Available only for oral use. Dosage is 0.25-1.0 Gm q 6 h.

3. *Toxicity, Side Effects and Precautions:* Same as for cloxacillin.

4. *Miscellaneous:* Peak serum levels approximately twice those with cloxacillin at comparable dosage.

E. *Nafcillin (Unipen):*

1. *Spectrum and Uses:* Similar to oxacillin.

2. *Routes of Administration and Dosage:*

a. Oral—absorption not reliable.

b. Intramuscularly—0.5 Gm q 4-6 h.

c. Intravenously—0.5-1.0 Gm q 4 h. May be administered by method described for methicillin.

3. *Toxicity, Side Effects and Precautions:* As with oxacillin.

4. *Miscellaneous* — Significant biliary excretion.

IV. BROAD-SPECTRUM PENICILLINS:*

A. *Ampicillin (Penbritin, Polycillin):*

1. *Spectrum and Uses:*

a. Active vs most strains of *Proteus mirabilis* and occasional strains of other *Proteus* species. Active vs most strains of *H. influenzae, Salmonella* and *Shigella,* and about 50% of *E. coli* strains.

b. Similar to penicillin G in its activity vs Gram-positive cocci and vs anaerobes except that it is more effective vs many strains of enterococcus.

c. Susceptible to action of beta lactamase and therefore not effective vs most strains of *S. aureus.*

2. *Routes of Administration and Dosage:*

a. Oral—0.5-1.0 Gm q 4-6 h (probably best given one-half hour to an hour before meals).

b. Intramuscularly—0.5-1.0 Gm q 4-6 h.

c. Intravenously — 1.0-2.0 Gm or more

*These agents exhibit cross-allergenicity with penicillin G. Probenecid blocks excretion of all penicillins. All are bactericidal.

q 4 h; may be administered in the same way as recommended for methicillin.

3. *Toxicity, Side Effects and Precautions:*

a. Sensitivity reactions as with penicillin G.

b. Bone marrow depression.

c. SGOT elevation (occasional).

d. Diarrhea (may be fulminant).

e. Moniliasis and other superinfections are more frequent than with other (narrower spectrum) penicillins.

4. *Miscellaneous* — Significant biliary excretion.

V. CEPHALOSPORINS:

A. *Cephalothin (Keflin):*

1. *Spectrum and Uses:*

a. Active vs most strains of *P. mirabilis* and some strains of other *Proteus* species and vs most strains of *Salmonella* and *Shigella.* Active vs approximately 50% of strains of *Klebsiella-Enterobacter* and *E. coli.* It is not particularly active vs *H. influenzae.*

b. Similar to penicillin G in its activity vs Gram-positive cocci other than *S. aureus* but less active vs pneumococci. It is less active vs most anaerobes.

c. Resistant to beta lactamase and therefore effective vs penicillin-resistant *S. aureus.*

2. *Routes of Administration and Dosage:* Not acid-stable; must be given parenterally.

a. Intramuscularly—0.5 Gm q 6 h for average case. Up to 1.0 Gm q 4 h in severe or relatively resistant infections.

b. Intravenously—0.5 Gm q 6 h to 2.0 Gm q 3 h or more. May be administered by method described for methicillin.

3. *Toxicity, Side Effects and Precautions:*

a. Probably cross-allergenic with penicillins. Same type of side effects as with penicillins.

b. SGOT elevation (occasional).

c. Superinfections, particularly with *Pseudomonas.*

4. *Mode of Action*—bactericidal.

B. *Cephaloridine (Loridine):*

1. *Spectrum and Uses:*

a. Essentially the same as for cephalothin, except that it is more active against susceptible anaerobic organisms than is cephalothin.

2. *Routes of Administration and Dosage:* available only for parenteral use.

a. Intramuscularly — 0.5-1.0 Gm q 6 h. Approved use of drug at the time of this writing restricts maximum daily dose to 4 Gm/day.

b. Intravenously—0.5-1 Gm q 6 h. May be administered by method described for methicillin. Maximum approved dose by this route is 4 Gm/day as well.

3. *Toxicity, Side Effects and Precautions:*

a. Nephrotoxicity has occurred when drug is administered in doses in excess of 4 Gm/day. This has usually occurred in patients with impaired renal function. However, all patients treated with this drug should be observed carefully and frequent urinalysis and serum creatinine levels should be obtained. This drug should not be used in patients with impaired renal function.

b. Cross allergenicity with cephalothin and possibly with penicillins as well.

c. Hematologic abnormalities — transient leukopenia, eosinophilia, hemolytic anemia (rare).

d. Superinfections, particularly *Pseudomonas.*

4. *Mode of Action*—bactericidal.

VI. STREPTOMYCIN:

1. *Spectrum and Uses:* Should never be used alone because of extremely rapid development of resistance by various bacteria. In combination with other agents, this drug is useful in tuberculosis, enterococcal infections, in endocarditis due to various organisms, in granuloma inguinale, and in *Pasteurella* infections.

2. *Routes of Administration and Dosage:* Intramuscularly—0.5-1.0 Gm q 12 h to 1.0 Gm 2-3 times weekly.

3. *Peak Blood Levels:* 20-40 mcg/ml after dose of 0.5-1.0 Gm.

4. *Toxicity, Side Effects and Precautions:*

a. Dermatitis (may be severe), drug fever.

b. Nephrotoxicity.

c. VIII nerve damage — primarily vestibular.

d. Bone marrow depression (uncommon).

e. Intraperitoneal, intrapleural, or rapid intravenous administration, particularly in association with ether anesthesia, may result in curare-like effect with respiratory paralysis. Neostigmine is the antidote of choice.

5. *Mode of Action:* Bactericidal.

VII. TETRACYCLINES:

1. *Spectrum and Uses:* Active against many Gram-positive and Gram-negative bacteria, vs rickettsiae, *Mycoplasma* and *Chlamydia* (Bedsonia). Most *S. aureus* are resistant. Twenty percent of Group A beta-streptococci are resistant, and occasional pneumococci are resistant.

2. *Routes of Administration and Dosage:*

a. Oral—

(1) Tetracycline, oxytetracycline, and chlortetracycline—250-500 mg q 6 h.

(2) Demethylchlortetracycline and methacycline—150 mg q 6 h or 300 mg q 12 h.

(3) Doxycycline—100 mg q 12 h x 3 doses, then 100 mg daily.

b. Intramuscularly—

(1) Tetracycline and oxytetracycline — 100 mg q 8-12 h.

(2) Rolitetracycline—350-700 mg daily in 1 or 2 injections.

c. Intravenously—

(1) Tetracycline, oxytetracycline, and chlortetracycline—500 mg q 8-12 h (by slow drip only).

(2) Rolitetracycline—350-700 mg q 12 h (over 15-30 minute period).

3. *Peak Blood Levels:*

a. Oral or Intramuscular—0.5-3.0 mcg/ml.

b. Intravenous—8-10 mcg/ml.

4. *Toxicity, Side Effects, and Precautions:*

a. Oral.

(1) Nausea, vomiting, anorexia, epigastric distress.

(2) Diarrhea, flatulence, proctitis.

(3) Stomatitis, glossitis.

(4) Dermatitis.

(5) Accumulation in teeth and bones — may cause pigmentation and enamel defects in teeth of children.

(6) Anaphylactoid reactions (rare).

(7) Phototoxic reactions (more common with DMCT).

(8) Vaginitis.

b. Intramuscular—local pain.

c. Intravenous.

(1) Thrombophlebitis

(2) Hepatotoxicity may be seen with daily doses exceeding 1.5 grams. With intravenous usage this may be accentuated (or found at lower dose levels) in the presence of impaired kidney function and/or pregnancy.

d. DMCT—May show, in addition to items listed above in 4. a, nephrogenic diabetes insipidus.

e. Special toxicity in the presence of impaired renal function (may be delayed).

(1) Increasing azotemia, acidosis, hyperphosphatemia.

(2) Anorexia, nausea, emesis.

(3) Weight loss.

(4) Increased urinary losses of nitrogen and sodium.

These effects may be avoided by reduced dosage. They are reversible. Anabolic steroids may prevent or retard these effects also.

f. Special toxicity with outdated drug—Fanconi syndrome may occur (reversible).

5. *Mode of Action:* Bacteriostatic.

6. *Miscellaneous:* The antibacterial activity of tetracycline is counteracted by certain multivalent metallic ions. Therefore, it is best to avoid concurrent administration of such things as aluminum hydroxide gel, milk, etc.

7. *Types of Tetracycline Preparations Available:*

a. Tetracycline (Achromycin, Cosa-tetracyn, Panmycin, Polycycline, Steclin, Sumycin, Tetracyn, Tetrex).

b. Oxytetracycline (Terramycin).

c. Chlortetracycline (Aureomycin).

d. Demethylchlortetracycline (Declomycin, DMCT).

e. Methacycline (Rondomycin).

f. Doxycycline (Vibramycin).

g. Rolitetracycline (Syntetrin, Velacycline).

These drugs are very similar chemically and biologically. There may be some quantitative differences in antibacterial activity against certain species or strains; oxytetracycline seems to be generally superior to the others against *Pseudomonas*. There is virtually complete cross-resistance between the various agents.

VIII. CHLORAMPHENICOL (Chloromycetin)

1. *Spectrum and Uses:* Active against many Gram-positive and Gram-negative bacteria, rickettsiae and *Chlamydia* (Bedsonia). Best drug for typhoid fever. In a number of localities, signficant numbers of staphylococci are resistant.

2. *Routes of Administration and Dosages:*

a. Oral—0.5 Gm q 6 h. Occasionally higher dosages are indicated.

b. Intramuscular—Must not be used by this route; absorption not dependable.

c. Intravenous — Chloramphenicol succinate 0.5 Gm q 4-6 h, each dose administered in 50 ml *over 15 minute period.*

3. *Peak Blood Levels:* 10-20 mcg/ml, by any of above routes.

4. *Toxicity, Side Effects and Precautions:*

a. Bone marrow depression (any or all elements); may be fatal. In rare instances, there is idiosyncratic bone marrow depression unrelated to dosage; apparently more common in white female children and after multiple courses. In most patients, however, toxicity is well correlated with dosage and blood levels and with duration of treatment. Elevation of serum iron and drop in reticulocyte count are early signs of toxicity. Complete blood counts should always be done at regular intervals.

b. "Gray syndrome" in premature and neonatal infants.

c. Optic or peripheral neuritis (rare).

5. *Mode of Action:* Primarily bacteriostatic.

6. *Miscellaneous:* There may be a greater hazard of toxicity in patients with impaired liver function. Biliary excretion is poor.

IX. MACROLIDES:

A. *Erythromycin (Erythrocin, Ilosone, Ilotycin):*

1. *Spectrum and Uses:* Active against Gram-positive organisms primarily. Fifteen percent or more of *S. aureus* strains are resistant in some areas. Usefulness in staphylococcal infections (as a single agent) limited by initial resistance or development of resistance. Also useful in *Hemophilus* and *Mycoplasma* infections.

2. *Routes of Administration and Dosage:*

a. Oral or Intravenous—0.5 Gm q 6 h.

b. Intramuscular — 100 mg q 8-12 h. Give *deep* intramuscularly.

3. *Peak Blood Levels:*

a. Erythromycin base or stearate (Ilotycin, Erythrocin) 0.5-3.0 mcg/ml.

b. Erythromycin estolate (propionyl erythromycin lauryl sulfate, Ilosone)—Levels 2-3 times those with erythromycin base or stearate and more consistent. This compound is available only for oral administration.

4. *Toxicity, Side Effects, and Precautions:*

a. Diarrhea, occasional nausea and vomiting.

b. Mild rash (infrequent).

c. Anaphylaxis (rare).

d. Intrahepatic cholestasis with jaundice is seen occasionally in patients on erythromycin estolate. Eosinophilia (in the peripheral blood) occurs with this. The syndrome is a hypersensitivity phenomenon, occurring typically when the drug is taken for 10 days or more or in repeated courses. The symptoms may recur, in sensitive patients given another course, within 48 hours or even after a single dose.

e. Intramucular injection usually *very* painful.

5. *Mode of Action:* Bacteriostatic

B. *Oleandomycin, triacetyloleandomycin (Cyclamycin, Matromycin, TAO):*

These agents have similar activity and there is marked cross-resistance between them and erythromycin as well. Erythromycin is significantly more active than these drugs and since resistance develops relatively easily to any of these agents, the other agents should not be used except under very unusual circumstances where it is demonstrated that an organism is sensitive to one of them and not to erythromycin and another better agent is not available.

Both intrahepatic cholestasis and hepatocellular abnormality occur with triacetyloleandomycin; a significant percentage of patients receiving 1 Gm/day for over two weeks may show such changes. Oleandomycin shows little toxicity.

X. LINCOMYCIN (Lincocin):

1. *Spectrum and Uses:* Active against Gram-positive coccal organisms (including most strains of *S. aureus*) and anaerobes (with the exception of *Bacteroides fragilis*). No activity against *H. influenzae.* Moderate activity vs. *Mycoplasma.*

2. *Routes of Administration and Dosage:*

a. Oral—0.5-1.0 Gm q 6 h.

b. Intramuscular—600 mg q 12 h.

c. Intravenous—600 mg q 6-8 h.

3. *Peak Blood Levels:*

a. Oral—3-5 mcg/ml

b. Parenteral—6-13 mcg/ml.

4. *Toxicity and Side Effects:*

a. Diarrhea.

b. Occasional nausea, emesis or abdominal distress.

c. Occasional rash or urticaria.

d. Local reactions to intramuscular injection (inflammation).

e. Neutropenia—rare, reversible.

f. Abnormal SGOT levels (occasional).

5. *Miscellaneous:* One-way cross-resistance with erythromycin; strains of *S. aureus* resistant to lincomycin are also resistant to erythromycin.

XI. NOVOBIOCIN (Albamycin):

1. *Spectrum and Uses:* Sometimes useful in *Proteus* (particularly *P. mirabilis* and *P. vulgaris)* infections. Should not be used for pneumococcal or streptococcal infections. Rarely of use in treatment of staphylococcal infections at the present time.

2. *Routes of Administration and Dosage:*

a. Oral—0.25 to 0.5 Gm q 6 h or 0.5-1.0 Gm q 12 h.

b. Intramuscular or intravenous — Same as for oral. *Incompatible with dextrose-containing solutions.* Give slowly intravenously.

3. *Peak Blood Levels:* 20-40 mcg/ml; considerable protein binding.

4. *Toxicity, Side Effects, and Precautions:*

a. Neutropenia—typically mild and reversible. Pancytopenia reported rarely. Hemolytic anemia—rare.

b. Rashes — incidence 10-20%. Occur after 7th to 9th day. May be readily managed with antihistamines as a rule.

c. Urticaria, drug fever, eosinophilia.

d. Appearance of a yellow pigment in the plasma (which may interfere with the determination of serum bilirubin and icteric index) may mask evidence of true liver damage and is therefore an indication for discontinuing the drug.

e. In neonates and young infants, there may be interference with conjugation of bilirubin.

5. *Mode of Action:* Usually bacteriostatic.

6. *Miscellaneous:* There is relatively poor distribution in tissues.

XII. KANAMYCIN - NEOMYCIN - PAROMOMYCIN GROUP:

A. *Kanamycin (Kantrex):*

1. *Spectrum and Uses:* Safest of group for parenteral administration. Poorly absorbed orally; oral usage is for intestinal infections or for "bowel sterilization." Very effective against a wide variety of Gram-positive and Gram-negative organisms. Ineffective, or relatively so, against *Pseudomonas,* streptococci, pneumococci, anaerobes, *Brucella.* Some Klebsiella-Aerobacter strains are resistant. A significant number of *S. aureus* strains at many institutions are extremely resistant. This resistance is high enough to exceed concentrations of drug used topically or achieved in G.I. tract after oral administration.

2. *Routes of Administration and Dosage:*

a. Intramuscular — 15 mg/kg/day or less (usually 1 Gm/day or less). Divided into 2-4 doses.

b. Intravenous — same as intramuscular. Give very slowly. Avoid this route entirely, if possible, particularly in presence of impaired renal function.

c. Oral—1.5 Gm q 4-6 h. Loading dose of 1.0 Gm q h x 4 may be used when rapid effect is desired. Some workers prefer to never exceed 4.0 Gm/day orally.

3. *Peak Blood Levels:*

a. Parenteral—20-35 mcg/ml.

b. Oral—negligible except with severe hepatic disease, renal disease, or in the presence of extensive bowel ulceration.

4. *Toxicity, Side Effects, and Precautions:*

a. Nephrotoxicity—azotemia is chief manifestation. Seen more often in patients with pre-existing impairment of renal function. Recovery slow (4-6 weeks) but apparently complete as judged by the usual clinical determinations. Seen in older patients in absence of obvious evidence of pre-existing impaired renal function.

b. Ototoxicity — both branches of VIII nerve may be involved, but primarily the auditory. Related to dosage, blood level, duration of therapy, impaired renal function (pre-existing or caused by drug), and previous perceptive hearing loss. May occur even with oral therapy in patients with poor renal function, etc. More likely to occur with concomitant or *sequential* use of other ototoxic agents. Essentially irreversible. Observe patients closely for such early evidences of ototoxicity as tinnitus, "fullness" in the ear, and/or audiometric evidence of loss of acuity. Loss of acuity at 4000 and 8000 cycles typically occurs before subjective hearing loss.

c. Pain at injection site occasionally—usually prevented by procaine.

d. Curare-like effect with respiratory paralysis or arrest—may follow intraperitoneal, intrapleural, or rapid intravenous administration, particularly in association with ether anesthesia. Calcium gluconate or neostigmine should be tried as antidotes.

e. Since kanamycin is dialyzable, consideration should be given to utilizing dialysis promptly in patients with early evidence of toxicity.

B. *Gentamicin (Garamycin):*

1. *Spectrum and Uses:* Active against most Gram-negative bacteria including *E. coli, Pseudomonas aeruginosa* and *Proteus* species. Kanamycin is more active against *Proteus* species and some strains of Klebsiella-Enterobacter but gentamicin is effective against some strains of Klebsiella-Enterobacter which are resistant to kanamycin. It is the drug of choice for serious *Pseudomonas* infections, recognizing that occasional strains may be resistant. Its role in the management of staphylococcal infection remains to be defined. It is ineffective against streptococci, pneumococci, and anaerobes.

2. *Routes of Administration and Dosage:*

a. Intramuscular—0.4-1.0 mg/kg q 8 h. In serious infections, doses of 1.5 mg/kg q 8 h have been used for limited periods.

b. Topical.

3. *Peak Blood Levels:* With normal renal function, doses indicated do not usually produce serum levels in excess of 10 mcg/ml.

4. *Toxicity, Side Effects, and Precautions:*

a. Similar to that indicated for kanamycin.

b. Ototoxicity — both branches of VIII nerve may be involved, but the vestibular branch is involved more often. Predisposing factors as described under kanamycin probably apply to this drug as well.

C. *Neomycin (Mycifradin):*

1. *Spectrum and Uses:* Very similar to kanamycin. Should not be used parenterally because of greater toxicity. Cross-resistance with other members of group may be seen.

2. *Routes of Administration and Dosage:*

a. Oral—as with kanamycin.

b. Topical—5 mg/ml or Gm. Caution: large volumes of irrigating fluid or prolonged administration may produce enough absorption to cause toxicity.

3. *Peak Blood Levels:*

Oral — negligible, except in patients with severe hepatic failure, renal disease, or extensive bowel ulceration.

4. *Toxicity, Side Effects, and Precautions:* Qualitatively similar to kanamycin, but more toxic. Here, neostigmine is probably antidote of choice for neuromuscular block. Deafness may progress for extended periods after therapy has been stopped and blood levels are no longer demonstrable.

5. *Mode of Action:* Bactericidal.

D. *Paromomycin (Humatin):*

Similar to kanamycin and neomycin and shows cross-resistance with them. Used only orally. May be more effective in intestinal amebiasis than related compounds.

XIII. POLYMYXIN-COLISTIN GROUP:

A. *Polymyxin B Sulfate (Aerosporin):*

1. *Spectrum and Uses:* Effective vs. most Gram-negative bacilli other than *Proteus.* Diffuses poorly into body cavities and tissues. Susceptible to inactivation by constituents of cells and tissues. Orally, there is very little absorption so it is useful for some enteric infections.

2. *Routes of Administration and Dosage:*

a. Intramuscular — 2.5 mg/kg body weight/day; give in 3 divided doses (q 8 h). Average dosage is 50 mg q 8 h intramuscularly. May be diluted with procaine.

b. Oral — 10-20 mg/kg/day, divided into 4 doses (not absorbed).

c. Intravenous—Same dosage as intramuscular, but never over 200 mg per day. Administer each dose over 60 to 90 minute period.

d. Topical—0.1 to 0.25% concentration.

e. Intrathecal — Treatment of choice for *Pseudomonas* meningitis. 5-10 mg in 10 ml of N/S first day, then 5 mg daily for 3 days, then 5 mg every other day.

3. *Peak Blood Levels:* About 2 mcg/ml.

4. *Toxicity, Side Effects, and Precautions:*

a. Nephrotoxicity; rising creatinine is indication for lowering dosage or discontinuing drug. Renal shutdown rare. Changes usually reversible, as far as is known.

b. Neurotoxicity — Paresthesias, ataxia, weakness of legs, dizziness. Entirely reversible, but may be disturbing enough to patient to force cessation of treatment.

c. Very painful on injection for most patients.

d. Drug fever.

e. The possibility of neuromuscular blockade with respiratory paralysis should be kept in mind when this agent is used intraperitoneally, intrapleurally, or intravenously. Calcium gluconate counteracts this effect experimentally.

B. *Colistin methanesulfonate (Coly-Mycin):*

Similar to polymyxin B. Should not be used intravenously or intrathecally (contains dibucaine). Intramuscular dosage—5.0 mg/kg per day in divided doses (q 6 h). Much less pain at intramuscular injection sites. (However, polymyxin given intravenously avoids this problem.) Toxicity comparable to polymyxin B when both are used at full therapeutic dosage. Currently more expensive than polymyxin B.

XIV. VANCOMYCIN (Vancocin):

1. *Spectrum and Uses:* Active against essentially all Gram-positive organisms; ordinarily should be reserved for infections not readily treatable with less toxic agents.

2. *Routes of Administration and Dosage:*

a. Oral — 4 grams/day. Absorption negligible, so useful only for staphylococcal enterocolitis.

b. Intravenous — Parenteral administration must be by the intravenous route. Dosage—2 Gm daily, preferably 1 Gm q 12 h in volume of 50-100 ml administered over 15-30 minutes.

3. *Peak Blood Levels:* 5-20 mcg/ml.

4. *Toxicity, Side Effects, and Precautions:*

a. Thrombophlebitis — less common when given intermittently rather than by constant intravenous drip.

b. Rash, urticaria, drug fever.

c. Anaphylactoid reactions—rare.

d. Nephrotoxicity — particularly in patients with previous impairment of renal function.

e. Ototoxicity—much less frequent than with kanamycin. Related to high blood levels, whether due to impaired renal function or not.

f. Leukopenia (rare).

5. *Mode of Action:* Bactericidal.

6. *Miscellaneous:* It appears to be very difficult to induce resistance to this drug either *in vitro* or *in vivo.*

XV. BACITRACIN:

1. *Spectrum and Uses:* Active against Gram-positive organisms primarily. Rarely used parenterally at present.

2. *Routes of Administration and Dosage:*

a. Parenteral — 50,000 to 100,000 units daily, divided into 4 doses (q 6 h) intramuscularly. Should be diluted in procaine in normal saline. Give *deep* intramuscularly.

b. Intrathecal — 5,000 to 10,000 units in normal saline daily (for staphylococcal meningitis). Very well tolerated by CNS.

c. Topical—500 to 1,000 units/ml or Gm.

3. *Peak blood levels* after parenteral use—0.3 to 3.0 units/ml.

4. *Toxicity, Side Effects, and Precautions:*

a. Pain at injection site.

b. Nephrotoxicity — renal tubular necrosis may occur. If patient's blood urea nitrogen or creatinine is normal and remains so, toxicity will usually be minimal and reversible. Watch urinary output carefully.

5. *Mode of Action:* Bactericidal.

XVI. NITROFURANS:

A. *Nitrofurantoin (Furadantin)*

1. *Spectrum and Uses:* Useful only for urinary tract infections. Most urinary tract infections with *E. coli,* staphylococci and enterococci respond. About 50% of infections due to *Proteus* species or Klebsiella-Enterobacter respond. *Pseudomonas* is resistant and may cause superinfection.

2. *Routes of Administration and Dosage:*

a. Oral—50-100 mg q 6 h.

b. Intravenous (Furadantin sodium)—180 mg in 500 ml of diluent q 12 h (60 drops/minute). Reduce dosage for patients under 120 lbs. Dissolve crystals just prior to use.

3. *Blood Levels:* Negligible.

4. *Toxicity, Side Effects, and Precautions:*

a. Nausea, vomiting—minimized by taking drug with food.

b. Headache, malaise, dizziness.

c. Rash, urticaria, other sensitivity reactions (including pulmonary infiltrates).

d. Hemolytic anemia in certain susceptible patients (people with red cells having glucose-6-phosphate dehydrogenase deficiency).

e. Peripheral neuritis — particularly in patients with impaired renal function or predisposition to neuritis (diabetes, avitaminosis, etc.).

5. *Mode of Action:* Primarily bacteriostatic.

6. *Miscellaneous:* Macrodantin is a macrocrystalline form of nitrofurantoin which is probably comparable in activity and which may offer the advantage of fewer gastrointestinal side effects.

B. *Furazolidone (Furoxone):*

1. *Spectrum and Uses:* This nitrofuran is used for treatment of enteric disease due to *Shigella* and *Giardia.*

2. *Route of Administration and Dosage:* 100 mgm orally q 6 h.

3. *Toxicity, Side Effects, and Precautions:*

a. Reactions similar to those described for nitrofurantoin.

b. Disulfiram-like reactions may occur after alcohol in patients on this drug.

c. Urine may turn brown (not a sign of toxicity).

4. *Blood Levels:* Drug absorbed poorly; blood levels very low.

XVII. NALIDIXIC ACID (NegGram):

1. *Spectrum and Uses:* Useful primarily for urinary tract infections. May be useful in therapy of *Shigella* and enteropathogenic *E. coli* enteritis and the *Salmonella* carrier state, but available studies are not adequate to allow one to properly judge its place in the management of these conditions. In the case of urinary tract infection, it is most useful against *Proteus* but may also be useful in infections due to *E. coli,* Klebsiella-Enterobacter and occasionaly strains of *Pseudomonas,* staphylococci and enterococci.

2. *Routes of Administration and Dosage:* Available only for oral use. The usual initial dose is 4.0 Gm/day given in four divided doses. If therapy is continued for longer than 7-10 days, dosage should be reduced to 2.0 Gm/day.

3. *Toxicity, Side Effects, and Precautions:*

a. Nausea, emesis, occasionally diarrhea.

b. Rash, urticaria, drug fever, eosinophilia, photosensitivity.

c. Occasional elevation of SGOT.

d. Occasional neural disturbances — headache, drowsiness, dizziness, visual disturbances, acute toxic psychosis, convulsions.

XVIII. AMPHOTERICIN B (Fungizone):

1. *Spectrum and Uses:* Effective against both North and South American blastomycosis, histoplasmosis, moniliasis, sporotrichosis, cryptococcosis (torulosis), aspergillosis, mucormycosis and coccidioidomycosis.

2. *Routes of Administration and Dosage:*

a. Intravenous — Start with daily dose of 5 mg and increase gradually (by 5-10 mg/day) to maintain dosage of 50-70 mg every other day. Drug must be administered in 5% dextrose *in water* using 100 to 150 ml of solution for each 10 mg of drug. Administer over not less than 6 hour period, using small gauge needle. Analgesics, antihistamines, sedatives, etc. may be used to minimize reactions. Total dosage should not exceed 2.0-3.0 Gm, if possible.

b. Intrathecal or intraventricular* — Dilute drug in sterile distilled *water* to a concentration of 0.25 mg/ml. The initial dose should not exceed 0.1 mg. This should be administered slowly after first diluting solution with 6-8 volumes of spinal fluid. Increase dosage at rate of 0.1 mg for each subsequent injection to maximum of 0.5-0.7 mg. Solutions must be made fresh each time. Injections should be given 3-4 x weekly, preferably alternating between lumbar and cisternal sites after the first few lumbar injections. Ordinarily, this schedule is followed for approximately one month and then maintenance injections of 0.5 mg are given intracisternally once weekly for at least two more months. Intraventricular therapy may be used in place of lumbar or cisternal intrathecal therapy.

c. Topical—Amphotericin may also be used locally in the pleural space, joints, directly into superficial lesions, etc., in selected cases.

3. *Toxicity, Side Effects, and Precautions:*

a. Fever, chills, headache, nausea, vomiting.

b. Phlebitis.

c. Anemia; requires transfusion at times.

d. Nephrotoxicity—Unique nephropathy involving hyperkaluria, nephrocalcinosis and other features suggestive of renal tubular acidosis. Decreased glomerular perfusion is another feature. Renal toxicity probably best followed by endogenous creatinine clearance.

e. Arachnoiditis may follow intrathecal therapy.

*Repeated intraventricular injection is feasible only when a device such as an Ommaya valve has been implanted surgically.